REMARKS

New claims 76-78 are pending. Claims 1-75 have been cancelled without prejudice. Applicant reserves the right to prosecute subject matter withdrawn from consideration by cancellation in one or more continuation, continuation-in-part, or divisional applications.

New claims 76-78 are fully supported by the instant specification. Thus no new matter has been added.

The Invention

New claims 76-78 are directed to recombinant Fab fragments of antibodies (rVabs) connected to a small peptides (Pep) - the complex being called rVab-Peps. The rVab portion of the complex comprises variable and constant regions from immunoglobulin light and heavy chains to form a Fab fragment that can bind to a pharmacological target. The rVab does not just bind anywhere on the target, but rather binds to the target at an active surface (also known as a determinant). An active surface or determinant is a specific binding region of the target that is required to be bound to in order for the target to effect its biological response. For example, receptor molecules can be large polypeptides. However, the endogenous ligand actually binds to and physically touches only a small portion of the receptor polypeptide. These small portions are referred to as active surfaces or determinants (see, e.g., paragraphs 50, 52, 94 and 95 of US Publication 2004/0072271). In rVab-Peps, the peptide portion also binds to an active surface or determinant. Thus, two different active surfaces or determinants of the target are bound to by an rVab-Pep.

The rVab-Peps are made by modifying the gene encoding an rVab such that it now also encodes a small amino acid sequence that is in frame to one end of either the heavy

or light chain of the rVab. In some embodiments, the small peptide is attached to both the heavy and light chain of the rVab.

rVab-Peps can be used to isolate small organic molecule replacements (also known as SOMERS, see, e.g., paragraph 108 of US Publication 2004/0072271) that bind to the target through its active surfaces such that a biological response is caused by (e.g., agonized) or inhibited by (e.g., antagonized) the binding. Because the smaller active site has been isolated using the methods of the invention, the SOMER can be much smaller and less complex than conventional agonists/antagonists because only the relevant portion of the target need be bound. Targets with more than one active surface may need more than one active surface to be bound by a SOMER in order to have an effect. More than one SOMER can be linked together to form the agonist/antagonist such that multiple active surfaces are bound. In embodiments where there are two SOMERS linked, the molecule is called a DISOMER (see, e.g., paragraphs 136 and 473 of US Publication 2004/0072271). In some embodiments, small molecule libraries can be screened for those compounds that have the ability to displace the rVab-Pep at one or more of the active surfaces. Examples 3 (paragraphs 470-508 of US Publication 2004/0072271) and 4 (paragraphs 509-516 of US Publication 2004/0072271) show the use of rVab-Peps to isolate DISOMERS and TRISOMERS, respectively, for growth hormone receptor.

The Examiner has interpreted the claimed invention as any antibody conjugated to any peptide wherein both the antibody and the peptide molecule bind to the same target (see page 4, lines 18-21 of the Office Action mailed June 14, 2006). Applicant respectfully disagrees with the Examiner's characterization of the claims. As stated *supra*, the components of the rVab-Pep do not just bind to anyplace on the target. Rather, each component must bind to a separate determinant on the target. Additionally, the rVab

component is not required to be a complete antibody. Rather, it can be a Fab fragment composed of one each of a variable domain of a heavy chain, a variable domain of a light chain, a constant domain of a heavy chain, and a constant domain of a heavy chain (see Figure 2A of US Publication 2004/0072271 for antibody structure schematics).

Priority

The Examiner alleges that the invention clamed in the pending claims are not supported by the earliest filed application – namely US Patent Application Serial No. 08/286,084 (hereafter "the '084 application"). Applicant respectfully disagrees.

The Examiner points out that the terms "rVab" and "rVab-Pep" are not found in the '084 application and thus does not disclose the claimed subject matter. Applicant concedes that the terms may not be in the specification of the '084 application but the concept of the invention in the pending is there. For example, rVabs are disclosed as follows:

> Reagents are provided by this invention which are suitable for identifying active sites on pharmaceutical targets. The reagents comprise libraries of variable regions of antibodies (V_{ab}) which are used to prepare recombinant Fab fragments useful for scanning the surface of a target in a manner so as to identify those Fab's having desired potency, activity, specificity and selectivity.
>
> (page 14, lines 1-8 of Application Serial No. 08/286,084).

Moreover, rVab-Peps are disclosed as follows:

> This invention solves the problem by first creating bivalent VAb which allow for the isolation of bivalent active VAb surface reporters capable of identifying each receptor subunit endogenous ligand attachment site. In this process, identification of bifunctional active surface reporters, proceeds by taking a plurality of members of each group of VAbs which have previously been identified as recognizing a particular limited surface of one of the target's subunits, or a larger number of one or two selected groups encompassing aa which are known to be involved with subunit I endogenous ligand binding functions and *fusing to their heavy chain constant domain a piece of DNA which encodes in frame a flexible aa linker followed by a library of small random decapeptides to create a bifunctional reporter (biFab(tarI)PEPLIB)*

consisting of one VLCL and one VHCH1-linker-PEP[10] where the Fabs recognize subunit I target surfaces. (emphasis added)
(page 23, lines 12-29 of Application Serial No. 08/286,084)

Although different terminology is used (i.e., biFab(bsI)PEP), there is disclosure of a Fab fragment fused to a peptide as is in an rVab-Pep.

Not only is there disclosure of the claimed invention, but that disclosure would satisfy the written description requirement. According to applicable case law, "ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996). Furthermore, according to MPEP 2163.07 (6th ed., Rev. 3, July 1997), "Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible."

In view of the foregoing, applicant respectfully requests that the rejection of the priority claim is reconsidered and withdrawn.

Rejections Under §112

Claims 47-50 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that a number of terms in the claims are indefinite. Applicant respectfully disagrees.

The Examiner alleges that the term "rVab" is vague and indefinite. As currently pending, the claims encompass rVabs comprising certain specific portions of immunoglobulin domains (i.e., variable and constant regions from immunoglobulin light and

heavy chains). The instant specification defines the term rVab as referring to recombinant Fab fragments (see paragraph 36, lines 3-10 of US Publication 2004/0072271). Moreover, what is meant by the term rVab is further described in a number of places (see, e.g., paragraphs 65 and 260 of US Publication 2004/0072271). Although the term rVab may not be used universally be the scientific community to refer to a particular structure, applicant has consistently used the term in the specification and described its meaning. A patentee can be his own lexicographer. Loctite Corp. v. Ultraseal Ltd., 228 U.S.P.Q. 90 (C.A.F.C. 1985) citing Autogiro Co. of American v. United States, 384 F.2d 391, 397, 155 U.S.P.Q. 697, 702 (Ct. Cl. 1967). As such, one skilled in art reading the specification would know what is meant by "rVab".

The Examiner alleges that the preamble of claim 47 is indefinite. New claim 76 more clearly states what is encompassed by the present invention. Specifically, an rVab-Pep is claimed that can be used in the methods of the invention to isolate SOMERS. As such, one skilled in the art would understand what is being claimed.

The Examiner alleges that the term "determinants" is confusing. Applicant has used the term in the specification to mean an active surface that is a specific binding region of the target that is required to be bound to in order for the target to effect its biological response the target at an active surface (see, e.g., paragraphs 50, 52, 94 and 95 of US Publication 2004/0072271). Although the term determinant may not be used universally be the scientific community to refer to a particular structure, applicant has consistently used the term in the specification and described its meaning. A patentee can be his own lexicographer. Loctite Corp. v. Ultraseal Ltd., 228 U.S.P.Q. 90 (C.A.F.C. 1985) citing Autogiro Co. of American v. United States, 384 F.2d 391, 397, 155 U.S.P.Q. 697, 702 (Ct.

Cl. 1967). As such, one skilled in art reading the specification would know what is meant by "determinant".

The Examiner alleges that the term "biological response" is indefinite. New claim 76 recites the term "biological activity". The biological activity observed when the one or more determinants are bound on a target varies with the target. Targets can be any number of molecules including, but not limited to, receptors, enzymes and structural components (see, e.g., paragraph 3, lines 16-17, paragraph 38, lines 7-12, and the Table after paragraph 516 of US Publication 2004/0072271). The targets bound to by the rVab-Peps according to the methods of the invention are not novel. One skilled in the art could readily go to the scientific literature to understand what biological activity is appropriate for their target of choice. Information which is well known in the art need not be described in detail in the specification. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80 (Fed. Cir. 1986).

The Examiner alleges that the terms "rVab component" and "rVab portion" are not clear as to if they are used interchangeably or if they are different. Applicant believes the rejection is moot because only the term "rVab component" is in the new claims and it is sufficiently defined such that one skilled in the art would know what is encompassed.

In view of the foregoing, applicant respectfully requests that the rejection under 35 U.S.C. § 112 is reconsidered and withdrawn.

Rejection Under §102

Claims 47, 48, and 50 are rejected under 35 USC §102(b) as being anticipated by Shin and Morrison, 1990, PNAS 87:5322 ("Shin and Morrison"). The Examiner alleges that the chimeric molecule disclosed in Shin and Morrison is encompassed by the pending claims. Applicants respectfully disagree.

Shin and Morrison describe an antibody having a light chain from a murine anti-dansyl antibody combined with a chimeric heavy chain. The heavy chain has the variable domain from the murine anti-dansyl antibody but has a constant region from a human antibody connected to insulin-like growth factor (IGF1). The chimeric antibody was shown to retain its specificity for dansyl binding as well as have the ability to bind the IGF1 receptor. The authors speculate that this type of antibody could be used to target tumors by replacing the anti-dansyl specificity of the antibody with an antibody that binds to a tumors-specific antigen (see page 5325, right column, lines 1-5 of Shim and Morrison). As such, the actual antibody described in Shin and Morrison does *not* bind tumors because dansyl is not a tumor antigen.

The chimeric antibody of Shin and Morrison is not encompassed by the pending claims for a number of reasons. First, the Shin and Morrison antibody does not bind a target as does the rVab-Peps of the invention. Each component of the rVab-Pep binds to different determinants of the *same* target. Conversely, the Shin and Morrison chimeric antibody binds dansyl and the IGF1 receptor. Dansyl is the 5-dimethylaminonaphthalene-1-sulfonyl radical that is used as a blocking agent for NH2 groups, e.g., during peptide synthesis. IGF1 receptor is a growth factor receptor. The two molecules are not in any way related and cannot be considered the same target. Second, the Shin and Morrison antibody does not bind a determinant as does the rVab-Peps of the invention. The IGF1 of the

chimeric antibody is the whole molecule that endogenously binds the IGF1 receptor. There are additional sequences present that are not directly responsible for binding to a determinant of the receptor. Third, the components of the Shin and Morrison antibody do not each bind a detrminant to effect biological activity as does the rVab-Peps of the invention. Although the IGF1 portion of the chimeric antibody does cause some amount of IGF1 receptor activity, that is the only component that binds to the receptor. The anti-dansyl portion of the antibody does not bind any determinants of the receptor and is thus not involved in eliciting the receptor activity. In contrast, each component of the rVab-Peps of the invention binds to the target and the binding of each is required to elicit the biological activity (as required by the claim).

"A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." In re Paulsen, 30 F.3d 1475, 31 USPQ2d 1671 (Fed. Cir. 1994). Clearly, the chimeric antibody of Shin and Morrison does not meet every limitation of the claimed invention.

In view of the foregoing, applicant respectfully requests that the rejection under 35 U.S.C. § 102 is reconsidered and withdrawn.

Rejection Under §103

Claims 47-50 are rejected under 35 USC §103(a) as being anticipated by Shin and Morrison in view of George et al., 1994, Journal of Immunology 152:1802 ("George"). The Examiner alleges that George remedies the deficinecy of Shin and Morrison – namely the description of conjugating a peptide molecule to the N-terminus of the VH region of an antibody. Applicant respectfully disagrees.

George describes single chain Fv molecules that bind to either the hapten DNP or the transferrin receptor. The single chain Fv molecules bound to cells expressing the appropriate antigen. A tag derived from c-myc was attached to the C-terminal end of the V region (see page 1804, right column, second to last paragraph). The Examiner cites Figure 1 as showing that the myc tag is attached to the N terminal region of the molecule, however, this is no error. Figure 1 shows the tag at the C-terminal end. Specifically, Figure 1C recites the N-terminal sequence of the scFv. One can see this sequence is present just behind the pelB leader sequence in Figure 2B – at the opposite end of the molecule from the myc tag.

Even assuming, en arguendo, that the myc tag is attached to the N-terminus, the scFvs of George still do not cure the deficiencies of Shin and Morrison to make the present invention obvious.

The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. In re O'Farrell, 853 F.2d 894, 902-4 (Fed. Cir. 1988); In re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. In re Dow Chemical Co., 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Again, as in Shin and Morrison, claim elements are missing such that the described scFvs are not encompassed by the currently pending claims. Even taken to together, the references do not teach or suggest the present invention.

In view of the foregoing, applicant respectfully requests that the rejection under 35 U.S.C. § 103 is reconsidered and withdrawn.

CONCLUSION

It is believed that the elected claims are in condition for allowance. Early and favorable action by the Examiner is earnestly requested.

AUTHORIZATION

No additional fee is believed due other than the extension of time submitted herewith. However, the Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 13-4500, Order No. 2598-4000US4.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

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